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Is Intraoperative Imprint Cytology Evaluation Still Feasible for the Evaluation of Sentinel Lymph Nodes for Lobular Carcinoma of the Breast?

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Abstract

Background—The evaluation of sentinel lymph nodes (SLNs) from a patient with lobular breast cancer is challenging. Metastatic lobular cancer is difficult to identify in SLNs because of its low-grade cytomorphology and its tendency to resemble lymphocytes. Intraoperative imprint cytology (IIC) is a rapid, reliable method for evaluating SLNs intraoperatively. We sought to reexamine our experience with this technique in the identification of invasive lobular breast cancer SLN metastases.

Methods—A retrospective review of a prospectively maintained database of IIC results of 1010 SLN mapping procedures for breast cancer was performed. From this cohort we reviewed SLN cases of lobular cancer. The SLNs were evaluated intraoperatively by bisecting the SLN. Imprints were made of each cut surface and stained with hematoxylin and eosin (H&E) and Diff-Quik. Permanent sections were evaluated with up to 4 H&E-stained levels and cytokeratin immunohistochemistry. IIC results were compared with final pathologic results.

Results—A total of 67 cases of pure invasive lobular cancer were identified. The sensitivity was 71%, specificity was 100%, and accuracy was 92%. No statistically significant differences in sensitivity, specificity, or accuracy were identified between the intraoperative detection of lobular carcinoma vs ductal carcinoma. The specificity has remained the same since 2004. However the accuracy (82% vs 92%; $P = .09$) and sensitivity (52% vs 71%; $P = .02$) has improved since 2004.

Conclusions—As we have previously shown, the sensitivity and specificity of IIC in evaluating lobular carcinoma is feasible and accurate. IIC continues to be a viable alternative to frozen section for intraoperative evaluation.

The disease status of the axillary lymph nodes is the most important prognostic factor for patients with breast cancer.^{1,2} Axillary lymph node dissection (ALND) provides good regional disease control and accurate pathologic staging. Thus, it is important for prognosis and in determining the need for adjuvant therapy.³ In the past, axillary lymph node status was evaluated by routine ALND; however, it is associated with considerable postoperative chronic morbidity including lymphedema, neurologic injury, joint stiffness, and, rarely, angiosarcoma.^{4–7} Sentinel lymph node biopsy (SLNB) is an accurate predictor of the overall axillary nodal status and has both a high sensitivity and specificity, especially when primary tumors are small.^{8–13} The minimally invasive technique of SLNB is less morbid than ALND

and allows for accurate pathologic staging of the axilla.¹⁴ SLNB is an acceptable standardized technique to evaluate the axilla in women with clinically negative axilla.¹⁵

Currently, intraoperative evaluation is performed using imprint or scrape cytology, frozen section histology, or a combination of these techniques.^{16–25} Although intraoperative immunohistochemistry and molecular techniques have been reported, they are not commonly used. Intraoperative imprint cytology (IIC) has been shown to be equivalent to frozen sections for rapid SLN evaluation. IIC is advantageous because it is rapid, reliable, less expensive, and tissue conserving. Furthermore, informing the surgeon about the presence of nodal metastases can decrease the number of second operations for nodal dissections especially in patients undergoing a mastectomy. Also, the patient and the family can be immediately aware of the sentinel lymph node status.

Compared with invasive ductal carcinoma, metastatic conventional invasive lobular cancer is difficult to identify in SLNs because of its low-grade nuclei and its tendency to infiltrate lymph nodes in a single cell pattern, thus resembling lymphocytes. We previously reported the use of imprint cytology (without intraoperative immunohistochemistry) in the evaluation of SLNs for lobular carcinoma, in 61 consecutive lymph node mapping procedures performed at both an academic medical center and a community hospital.²⁶ The level of diagnostic sensitivity and specificity of IIC are similar to that of intraoperative frozen section evaluation. IIC is therefore a viable alternative to frozen sections when intraoperative evaluation is desired. We seek to reexamine our experience with this technique in the evaluation of invasive lobular breast cancer sentinel lymph node metastases.

METHODS

We performed a retrospective review of a prospectively maintained institutional board of review approved database of SLN cases for breast cancer from May 1998 to July 2010. This produced 1010 SLN mapping procedures. From this cohort we reviewed SLN cases with invasive lobular carcinoma. A chart review of each SLN case was performed for the following data: age, sex, method of tumor detection, type of breast, and axillary surgical procedure. Primary tumor data included: size, type, and histologic grade. Tumor size was recorded according to the guidelines of the American Joint Committee on Cancer 7th Edition.²⁷ See Table 1 for tumor characteristics.

Surgical Protocol

A standard double indicator technique was used to identify the SLN. The patient's tumor bed was injected with filtered technetium sulfur colloid (0.5–1.0 mCi) preoperatively, until 2006 when subareolar injections became standard. A lymphoscintigram was rarely obtained at the surgeon's discretion in the Nuclear Medicine Department prior to the patient's arrival to the operative suite. A gamma probe (Neoprobe 2000, Neoprobe Corp., Dublin OH) was used intraoperatively to detect the SLNs. Periareolar injections of isosulfan blue were used intraoperatively to provide visual identification of the SLN in all cases. The SLNs were then harvested and sent fresh to pathology for intraoperative and permanent section evaluations. Complete ALND was performed only if the SLN contained tumor cells. A few of the patients were on cooperative group protocols which mandated lymphadenectomy regardless of the SLN result.

Pathologic Examination

Excised lymph nodes submitted for intraoperative evaluation were bisected along the long axis. Care was taken to obtain complete cross sections of the maximum diameter, preferably including the hilum and the marginal sinus. For each lymph node half, a pair of imprints was

made by gently touching the cut surface of the SLN to a glass slide. One imprint from each pair was air dried and stained with the Diff-Quik stain. The second imprint from each surface was immediately fixed in 95% ethanol for 3 min and then stained with hematoxylin and eosin (H&E) stain.

Imprints were reviewed intraoperatively by a board-certified pathologist. Diagnostic categories included positive or negative for tumor cells present in the SLN. The surgical team was subsequently notified of the result. Positive results prompted completion axillary lymphadenectomy, and a negative result indicated no further lymphatic dissection. Completion of the lymphadenectomy was performed if the sentinel lymph node was positive for metastatic disease. After an interpretation was rendered, the SLN was fixed in 10% formalin, processed in the usual manner, and paraffin embedded. A single H&E stained section of the SLN was cut from the paraffin block and examined. If initial review of the H&E stained section was negative, a SLN protocol consisting of an additional 3 H&E stained levels, cut at 50 micrometer intervals, in conjunction with immunohistochemical stains for cytokeratin (AE1/AE3, Dako, Carpinteria, CA), was performed on the first of the 3 levels. Immunohistochemical studies were carried out using the avidin-biotin-peroxidase complex (ABC) method described elsewhere.²⁸ Immunohistochemical stains for cytokeratin were considered positive if strong immunoreactivity in cell clusters or individual cells that demonstrated morphologic features of metastatic tumor cells were identified (see Fig. 1).

Statistics

Chi-square and Fisher exact tests (as appropriate) were used to assess differences in clinical and pathologic factors between those in our 2004 data and our current cohort and to assess the association between pathologic factors and IIC results. Sensitivity was defined as the percentage of positive IIC results among those with positive permanent pathology. Specificity was defined as the percentage of negative IIC results among those with negative permanent pathology. The false-negative rate was defined as the number of false-negative intraoperative imprint results divided by the sum of the false-negative and true-positive results. For the purposes of this manuscript, statistical significance was defined as a *P* value of less than .05.

RESULTS

SLN mapping was successful in 1010 mapping procedures. All cases with IIC diagnosis of the SLN were evaluated as per protocol. From this cohort of 1010 patients, 67 cases (6%) of pure invasive lobular carcinoma were identified. These patients ranged in age from 27 to 87 years (mean 60 years). Breast-conserving surgery or lumpectomy was performed in 55% of patients, and the remaining 45% underwent mastectomy, of which 46% of those chose a contralateral prophylactic mastectomy. The majority of tumors were stage 1. A summary of patient and tumor characteristics is detailed in Table 1.

From these 67 patients, a total of 125 SLNs were evaluated by intraoperative imprint cytology (average, 1.87 SLNs/patient). A separate intraoperative diagnosis was generated for each lymph node, and the results are reported on a per patient basis.

The accuracy of IIC compared with permanent section evaluation of the SLN for detection of lobular carcinoma was 92%. A total of 17 patients had positive SLNs by permanent section evaluation; of these, 5 were falsely negative by imprint cytology (sensitivity, 71%). All false negative patients had T2 estrogen receptor positive tumors. No false positive intraoperative diagnoses were identified (specificity 100%). No statistically significant differences in sensitivity, specificity, or accuracy were identified for the intraoperative detection of lobular carcinoma vs ductal carcinoma by imprint cytology (Table 2). When

comparing the data from our 2004 invasive lobular carcinoma series, we have seen improvements in both accuracy (82% vs 92%; $P = .09$) and sensitivity (52% vs 71%; $P = .02$) (Table 3). Similarly, we have seen improvement in the accuracy and sensitivity of IIC in ductal carcinoma cases. The specificity had decreased (Table 4). Finally there was no micrometastatic disease identified on permanent section for lobular carcinoma in our cohort. Detection rate of metastatic disease by imprint cytology was higher for macrometastatic disease (metastases ≥ 0.2 cm) than for micrometastatic ductal disease. IIC was negative in 13 cases with ductal carcinoma, but micrometastatic disease was found on final pathology, resulting in 31% of IIC missing micrometastatic disease.

DISCUSSION

Accurate intraoperative evaluation of SLN permits an ALND to be performed during the initial operation if the node is positive, thus saving the patient the time, cost, and burden of a second operation. We have shown this to be cost effective for IIC in breast cancer patients.²⁹ Several techniques can be used to examine the SLNs. A key advantage of the imprint cytology over frozen sectioning is the avoidance of the loss of tissue attendant to the use of a cryostat.³⁰ Thus, imprint cytology preserves much more tissue for subsequent focused pathologic analysis of the SLN.

However, the intraoperative detection of lobular carcinoma can be difficult. There has been a longstanding debate among pathologists that SLNs in invasive lobular cancer are more difficult to interpret. The intraoperative detection of lobular carcinoma is problematic because of its low-grade cytomorphology and its tendency to infiltrate metastatic sites in a single cell pattern. In our experience, because of the architectural and cytomorphologic features of metastatic lobular carcinoma, occasional large metastases are missed by intraoperative evaluation, only to be discovered, much to the surprise of the pathologist, on permanent H&E stained sections. This factor contributes significantly to the controversy that exists in this area. In the present study, no significant difference was observed between the sensitivity of detecting metastatic lobular carcinoma vs ductal carcinoma. These difficulties underscore the need for cytologic expertise when intraoperative SLN assessments are made. Cytologists are not available at all institutions, and the pathologic support available must be kept in mind when organizing a SLN program. Additionally, the specificity of this study was 100%, supporting the notion that false positive examinations, which would risk completion of an undesired completion ALND, are not a problem.

Furthermore, we found in comparison with our previous study that our accuracy and sensitivity has improved over time. This fact could be attributed to a learning curve due to our increased volume of cases. Our pathologists feel that this is due to more experience by mostly the same set of pathologists. They have learned to search more diligently for lobular carcinoma using different criteria from ductal cancer, such as identifying small nuclei, uniform cells in single layers as found in lobular cancer vs large nuclei, greater pleomorphism, and three-dimensional (3D) clusters of cells in ductal carcinoma.

Only 5 patients with invasive lobular cancers were found to have a false negative on IIC. Because so few patients were found to have a false negative, no statistical significance could be determined from this group. However, if you examine this cohort more closely, all 5 had T2 tumors that were estrogen receptor positive as the common denominator. N1 disease was seen in 60% of this group, the rest being N1. None of these patients underwent neoadjuvant chemotherapy. The only conclusion we can make about avoiding false negatives on IIC is to carefully inspect the SLN of patients with larger, T2, estrogen receptor positive tumors.

Other groups have looked at intraoperative detection of invasive lobular carcinoma with frozen section analysis. Horvath et al. recently demonstrated that the sensitivity (67% vs 75%; $P = .385$), specificity (100% vs 100%), and accuracy (86% vs 92%; $P = .158$) of IIC analysis of SLNs for patients with invasive lobular and invasive ductal carcinoma were comparable to those of frozen section.³⁰ They concluded that frozen section analysis of breast cancer patients should remain the standard of care. Several groups have also evaluated the use of intraoperative immunohistochemistry (IHC) in addition to frozen section and touch imprints cytology. Weinberg et al. analyzed 59 patients with invasive lobular carcinoma (ILC) using rapid intraoperative IHC on touch imprint cytology. They showed that their sensitivity was increased from 41.9% (without IHC) to 54.8% (with IHC) with rapid intraoperative IHC on touch preps.³¹ They concluded that intraoperative IHC on touch prep cytology enhances the intraoperative diagnosis of SLN metastases in patients with ILC. Leikola et al. examined sensitivity of the intraoperative diagnosis of SLN metastasis in 438 patients when using rapid IHC with a cytokeratin biomarker.³² The results were compared with those obtained for 557 patients without rapid IHC but with conventional staining. They showed that rapid intraoperative IHC on frozen section analysis improved the sensitivity of detecting metastatic disease from 66% (without IHC) to 87% (with IHC) for patients with lobular carcinoma ($P = .02$).³² However, we have previously shown that the cost for frozen section is significantly higher than for touch preps (SLN is \$135 touch prep vs \$356 for frozen sectioning), thereby, providing a cost-benefit savings for touch preps alone.²⁶

We have again demonstrated a poor sensitivity of IIC for detecting micrometastatic disease compared with macrometastatic disease. In the present study, the disparity between detection of micrometastatic disease vs macrometastatic disease was significant and parallels the discrepancy that exists for detection of metastatic ductal carcinoma by either frozen section or imprint cytology. Furthermore, touch imprint cytology sensitivity is dependent on the burden of disease on a bivalved lymph node.³³ Therefore, micrometastatic disease can easily be missed.

Lastly, how do we approach intraoperative imprint in light of the ACOSOG Z0011 data?³⁴ The trial enrolled patients with clinical T1 or T2N0M0 breast cancer treated with lumpectomy who were found to have 1 or 2 positive SLNs on standard pathologic examination and H&E staining. Patients with 3 or more positive SLNs were not eligible as were SLN metastases by IHC alone. Patients were required to have negative margins and to receive whole breast irradiation. They were randomized to undergo ALND or SLNB alone. At a medium follow-up of 6.3 years, there was minimal local recurrence (3.6% [ALND] vs 1.8% [SLN-only group]). There was no difference in overall survival (ALND 91% vs SLND-only 92.5%; $P = .24$) or disease-free survival (ALND 82% vs SLND-only 83.8%; $P = .13$) at 5 years.³⁴

From this data we have changed our practice to omitting ALND for those women who meet the eligibility requirement for the Z0011 trial.³⁵ Patients who undergo mastectomy, neoadjuvant chemotherapy, refuse radiation, or receive partial-breast irradiation are not eligible and must complete an ALND for a metastatic SLN. Furthermore, the MD Anderson group has eliminated routine intraoperative SLN assessment in patients who meet the Z0011 criteria.³⁵ We have also implemented this at our institution. However, IIC is important for patients who do not meet the Z0011 criteria, specifically those undergoing a mastectomy, partial breast radiation, or those who received neoadjuvant chemotherapy. The information gleaned from the IIC would save a second operation for a completion axillary dissection for a positive metastatic SLN. Hopefully, this decrease in volume will not affect the sensitivity, specificity, and accuracy of detecting metastatic disease in the intraoperative touch preps that we will still perform.

In summary, intraoperative detection of metastatic lobular carcinoma by imprint cytology is equivalent to that observed in ductal carcinoma. Furthermore we have shown that we have increased our sensitivity and specificity since 2004. In light of the pivotal ACOSOG Z0011 trial we anticipate less need for IIC in the future. However, we have found it particularly useful when immediate breast reconstruction with mastectomy is planned.³⁶ It remains to be seen if this decrease in volume of IIC will result in a decrement in the accuracy of SLN analysis.

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FIG. 1.

Two images of a positive imprint image on Diff-Quick of lobular carcinoma cells. Image 1 is at 400× magnification and image 2 is 600× magnification. Compared with the background lymphocytes, the tumor cells have higher nuclear to cytoplasmic ratios and deeply eosinophilic cytoplasm

TABLE 1

Patient and tumor characteristics for invasive lobular carcinomas

Age (years)	27–87 years (mean 60 years)
T stage	
T1	41 (61%)
T2	22 (33%)
T3	3 (5%)
T4	1 (0.1%)
Histologic grade	
Grade 1	21 (31%)
Grade 2	26 (39%)
Grade 3	7 (11%)
Unknown	13 (19%)
ER status	
Positive	59 (88%)
Negative	8 (12%)
PR status	
Positive	46 (69%)
Negative	21 (31%)
HER2/neu	
Positive	8 (12%)
Negative	59 (88%)
LVI	
Present	5 (7%)
Negative	62 (93%)

TABLE 2

Results of intraoperative imprint cytology evaluation relative to permanent section evaluation

Type of invasive carcinoma	No. of patients	No. of patients with + SLN on permanent	No of patients with + SLN by IIC	No. false + by IIC	Accuracy (%)	Sensitivity (%)	Specificity (%)
Lobular	67	17	12	0	92	71	100
Ductal	940	195	157	4	92%	70%	98%

TABLE 3

Comparison of 2004 and present data for intraoperative imprint cytologic evaluation of invasive lobular carcinoma

Time	Accuracy (%)	Sensitivity (%)	Specificity (%)
2004 data	82	52	100
2011 data	92	71	100%

TABLE 4

Comparison between 2004 and present day for intraoperative imprint cytology evaluation of invasive ductal carcinoma

Time	Accuracy (%)	Sensitivity (%)	Specificity (%)
2004 data	85	53	99
2011 data	92	70	98